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EXAMINER	
STRZELECKA, TERESA E	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 08/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/034,451	MIRKIN ET AL.	
	Examiner	Art Unit	
	Teresa E. Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-43,45-71 and 73-85* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-43,45-71 and 73-85* is/are rejected.

7)☒ Claim(s) *41 and 76* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/21/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 21, 2005 has been entered.

2. Claims 37-72 were previously pending. Applicants amended claims 37, 40-43, 45, 47, 48, 50, 52, 55, 64 and 69, cancelled claims 44 and 72 and added new claims 73-85. Claims 37-43, 45-71 and 73-85 are pending and will be examined.

3. Applicants' amendments overcame the following rejections: rejection of claims 48-51 under 35 U.S.C. 112, second paragraph; rejection of claims 37-40, 43, 46-51 and 72 under 35 U.S.C. 102(e) as anticipated by Abbott et al.; rejection of claims 41, 44, 45 and 69-71 under 35 U.S.C. 103(a) over Abbott et al. and Mirkin et al.; rejection of claims 55-68 under 35 U.S.C. 103(a) over Abbott et al. and Mirkin et al.; double-patenting rejection of claims 37-51 under 35 U.S.C. 101 over claims 40-47 and 50-55 of the co-pending application No. 10/158,543; double-patenting rejection of claims 37, 38, 40 and 42-46 under 35 U.S.C. 101 over claims 3-10 of the co-pending application No. 10/397,579.

4. Applicants' arguments regarding claim rejections are moot in view of new grounds for rejection.

Information Disclosure Statement

5. The information disclosure statement (IDS) submitted on June 21, 2005 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Priority

6. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 37-43, 45-71 and 73-85 of this application. The priority application No. 60/293,861, filed May 25, 2001 does not provide support for limitations of core/shell nanoparticles with magnetic cores and mean diameter of 5 to 150 nm. Therefore, the priority date of the instant claims is the filing date of the instant application, December 28, 2001.

Claim Objections

7. Claims 41 and 76 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 41 does not further limit claim 40, since it is drawn to a method of determining the thickness of the gold shell.

Claim 76 contains a limitation "wherein the magnetic core is magnetic", therefore it does not further limit the parent claim 69.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or

> with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 37-43, 45-71 and 73-85 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As stated in MPEP 2163.06:

"If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

The limitation added to claims 37 and 55 "the core/shell nanoparticle having a mean diameter ranging from 5 to 150 nm" is not supported by the specification or claims as originally filed. The only size of nanoparticles provided in the specification is ~12 nm (see, for example, page 2, line 22; page 4, line 4; page 10, line 29; page 11, line 2; page 13, line 7). Therefore, Applicants did not have a support for a limitation of nanoparticles ranging in size from 5 to 150 nm.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 82-84 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 82-84 are indefinite in claim 82. Claim 82 is indefinite over the recitation of "The method of claim 69 wherein nanoparticle-oligonucleotide conjugates are produced...". Since claim

69 is a method of nucleic acid detection using the nanoparticle-oligonucleotide conjugates, it is not clear how the conjugates can be produced by this method.

Claim Interpretation

12. Applicants did not define the term "nanoparticle", therefore this term is interpreted as a particle of any size.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 37-41, 43, 45-54, 69-71, 73 and 75-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Abbott et al. (U. S. Patent No. 6,277,489 B1; cited in the IDS and in the previous office action), Mirkin et al. (U.S. Patent No. 6,361,944 B1; cited in the IDS and in the previous office action) and Yguerabide et al. (Anal. Biochem., vol. 262, pp. 157-176, 1998; cited in the IDS).

> The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

A) Regarding claims 37, 41 and 47-51, Abbott et al. teach a multilayered material comprising a particulate substrate (= core), a metal film layered onto the substrate (= shell) and a recognition moiety attached to the metal layer (col. 4, lines 22-35). The particulate substrate may be any metal, selected according to desired properties, for example, being magnetic (col. 9, lines 55-67; col. 10, lines 1-6, 33-67; col. 11, lines 1-4). The particles can be of any size (col. 9, lines 63-65).

The particulate substrate is coated with a metal layer (= shell), such as gold, silver, platinum, palladium, nickel and copper, with gold being particularly preferred (col. 9, lines 3-13; col. 11, lines 34-55). An organic layer is attached to the metal layer and provides a link to the recognition moiety. The limitation of gold shell generated by a process of addition of gold salt and reducing agent to a solution containing the metal-containing core is a product-by-process limitation, but it is taught by Abbott et al. (col. 55, lines 59-67). Further, claim 41 does not add a structural limitation to claim 37, as it concerns the method of determining the thickness of a gold shell.

Regarding claim 38, Abbott et al. teach recognition moieties including biomolecules, such as nucleic acids (col. 12, lines 9-25; col. 16, lines 38-54; col. 19, lines 56-59).

Regarding claim 39, Abbott et al. teach oligonucleotides having reactive groups which can bind to nanoparticle (col. 22, lines 66, 67; col. 23, lines 1-5).

Regarding claims 40 and 73, Abbott et al. teach metal-containing cores comprising Fe or Ni (col. 10, lines 34-36).

Regarding claims 43 and 75, Abbott et al. teach metal oxides, for example Fe_2O_3, NiO (col. 10, lines 34-36).

Regarding claim 46, Abbott et al. teach at least one layer of the metal coating (col. 11, lines 44-46).

Note regarding rejection of claims 47-51: these are product-by-process claims, and it is not clear how the method of making a product of claims 47-51 and 72 makes the final product, i.e., a core-shell nanoparticle with oligonucleotide bound to it, different from the product of Abbott et al. (see MPEP 2113). Applicants added a limitation to claim 47 of addition of gold salt and reducing agent resulting in a reaction mixture having a gold salt concentration of about 2 μm. According to the specification (page 13, lines 12-14), such concentration inhibits the formation of gold cluster nucleation sites. However, it is not clear how this affects the structure of the final product.

MPEP 2113 Product-by-Process Claims

PRODUCT-BY-PROCESS CLAIMS ARE NOT LIMITED TO THE MANIPULATIONS OF THE RECITED STEPS, ONLY THE STRUCTURE IMPLIED BY THE STEPS.

"[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted) (Claim was directed to a novolac color developer. The process of making the developer was allowed. The difference between the inventive process and the prior art was the addition of metal oxide and carboxylic acid as separate ingredients instead of adding the more expensive pre-reacted metal carboxylate. The product-by-process claim was rejected because the end product, in both the prior art and the allowed process, ends up containing metal carboxylate. The fact that the metal carboxylate is not directly added, but is instead produced in-situ does not change the end product.).

Regarding claims 69 and 76, Abbott et al. teach a multilayered material comprising a particulate substrate (= core), a metal film layered onto the substrate (= shell) and a recognition moiety attached to the metal layer (col. 4, lines 22-35). The multilayered material may be used to capture a molecule in a purification process or an assay, and the captured molecule may be a nucleic acid (col. 24, lines 13-62). The multilayered material may be used to determine the presence or quantity of an analyte in a sample by contacting the sample with a multilayered material, forming a

complex between a recognition moiety and an analyte and detecting the analyte (col. 31, lines 44-63).

Regarding claims 78-81, Abbott et al. teach treating the inner metal-containing nanoparticle cores simultaneouslv with a solution comprising a gold salt and a solution comprising a reducing agent under conditions that produce a non-alloying gold shell surrounding the nanoparticle cores (Abbott et al. teach treating the core particles with a solution containing a gold salt, such as such as $Na_3Au(SO_3)_2$ and a reducing agent (col. 37, lines 6-38).

Regarding claims 80 and 81, Abbott et al. teach sodium borohydride, $NaBH_4$ (col. 37, line 36).

B) Abbott et al. do not teach nanoparticle core being magnetic, but they do teach that the metal cores may any metals or may be selected for their magnetic properties. Abbott et al. do not teach oligonucleotide densities of at least 10 picomoles/cm^2, or least 15 picomoles/cm^2, or from about 15 picomoles/cm^2 to about 40 picomoles/cm^2. Abbott et al. do not teach detection of nucleic acids bound to a surface or hybridization conducted in the presence of magnetic field.

C) Mirkin et al. teach detection of nucleic acids by hybridization using nanoparticle-oligonucleotide conjugates (Abstract).

Regarding claim 37, Mirkin et al. teach nanoparticles with sizes of 13 nm (col. 42, line 58; col. 46, line 36)

Regarding claims 45 and 77, Mirkin et al. teach nanoparticle-oligonucleotide conjugates used in nucleic acid detection methods (col. 2, lines 6-17). Mirkin et al. teach nanoparticles being magnetic (col. 16, lines 29-32), and Fe_3O_4 core nanoparticles with a silica shell, which can be conjugated to oligonucleotides (col. 33, lines 19-27).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used magnetic-core of Mirkin et al. in the nanoparticles of Abbott et al. The motivation to do so would have been that oligonucleotides attached to magnetic particles could be removed from solution by application of a magnetic field, allowing easy separation of hybridization products from solution.

Regarding claims 52 and 82, Mirkin et al. teach oligonucleotide surface density of at least 10 picomoles/cm^2 (col. 49, line 24).

Regarding claims 53 and 83, Mirkin et al. teach oligonucleotide surface density of at least 15 picomoles/cm^2 (col. 49, lines 26, 27).

Regarding claims 54 and 84, Mirkin et al. teach oligonucleotide surface density of at least 15 picomoles/cm^2 to no greater than about 35-40 picomoles/cm^2 (col. 49, lines 26-32).

Regarding claims 78 and 79, Mirkin et al. teach $HAuCl_4$ (col.42, lines 58-67).

It would have been *prima facie* obvious to one of ordinary skill in the art to have used nanoparticle conjugates with oligonucleotide density of at least 10 picomoles/cm^2 or at least 15 picomoles/cm^2 to no greater than about 35-40 picomoles/cm^2 of Mirkin et al. in the conjugates of Abbott et al. The motivation to do so, provided by Mirkin et al., would have been that a surface density of between 10 and 40 picomoles/cm^2 provided stable oligonucleotide conjugates (col. 49, lines 25-32).

Regarding claim 69, Mirkin et al. teach detection of analyte DNA bound to a surface, the method comprsing:

(a) contacting the surface with a solution comprising core/shell nanoparticle oligonucleotide conjugates of claim 37, wherein the nanoparticle core is magnetic, and wherein the contacting takes place under conditions effective to allow hybridization of the core/shell nanoparticle

oligonucleotide conjugates with the bound nucleic acid (Mirkin et al. teach contacting nanoparticle-oligonucleotide conjugates with analyte nucleic acid bound to a substrate (Fig. 13A; col. 2, lines 6-17; col. 19, lines 43-50; col. 21, lines 19-59). Mirkin et al. teach nanoparticles being magnetic (col. 16, lines 29-32).);

(b) subjecting the nanoparticle conjugate to an external magnetic field so as to accelerate movement of the nanoparticle conjugate to the surface to promote interaction between the nanoparticle conjugate and the nucleic acid (Mirkin et al. teach application of magnetic field (col. 33, lines 45 and 60, 61).);

(c) removing from the surface any nanoparticle conjugates that have not hybridized with the nucleic acid (Mirkin et al. teach washing unbound nanoparticle conjugates from the substrate (col. 21, lines 60-63).); and

(d) observing a detectable change brought about by hybridization of the nucleic acid with the nanoparticle conjugates (Mirkin et al. teach observing a detectable change brought about by hybridization (col. 22, lines 22-39 and 57-65).

Regarding claim 70, Mirkin et al. teach nanoparticles being magnetic (col. 16, lines 29-32), and Fe_3O_4 core nanoparticles with a silica shell, which can be conjugated to oligonucleotides (col. 33, lines 19-27).

Regarding claim 71, Mirkin et al. teach washing unbound nanoparticle conjugates from the substrate (col. 21, lines 60-63).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have combined magnetic-core particle hybridization of Mirkin et al. with analyte detection assays of Abbott et al. The motivation to do so would have been that oligonucleotides

attached to magnetic particles could be removed from solution by application of a magnetic field, allowing easy separation of hybridization products from solution.

D) Neither Abbott et al. not Mirkin.et al. teach nanoparticles with average size of 5-150 nm.

E) Yguerabide et al. teach use of submicroscopic light-scattering particles as labels in clinical and biological applications (Abstract; page 164, second and fifth paragraphs). Specifically, they teach that the extinction coefficient and its absorption maximum of nanoparticles varies with their size (Fig. 3; page 166, fourth paragraph), therefore allowing for tuning of their spectral properties according to their size. These particles also exhibit strong light-scattering properties (Fig. 4). Finally, they teach that sensitivity of detection of gold particles by scattering increases with their size as estimated by a number of fluorescein molecules which produce the same signal as one gold nanoparticle (Table 1; page 168, second paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used nanoparticles of different sizes of Yguerabide et al. in the methods of DNA detection by nanopaticle-oligonucleotide conjugates of Abbott et al. and Mirkin et al. The motivation to do so, provided by Yguerabide et al., would have been that "The light-producing powers of the 87- and 118-nm particles are equivalent to more than one million fluorescein molecules.." (page 168, second paragraph), and

"...Because we can detect a single particle in the field of the microscope objective, our sensitivity is usually limited by background signal due to nonspecific binding. However, we have found that nonspecific binding can be reduced to very low levels in our gold, light-scattering immuno- and DNA probe assays by the proper use and selection of stabilizing and blocking agents. Through these agents we have been able to achieve sensitivities which are better than, for example, a comparable ELISA and the procedures are much simpler and less expensive. In actual solid-phase assays with clinical samples (including fecal samples), we have been able to achieve sensitivities of 0.001 particles/mm2 on the transparent assay surface. In high-density microarray formats, we can

easily detect, by eye or with a video camera and microscope, gold particles in 20 x 20-μm assay squares, or larger squares, and achieve a wide concentration detection range. The signal from each square can be quantified by image analysis using steady state intensity or particle counting methods." (page 174, last paragraph; page 175, first paragraph).

15. No references were found teaching or suggesting claims 42, 55-68, 74 and 85, but they are rejected for reasons given above.

16. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E. Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

TERESA STRZELECKA
PATENT EXAMINER
Teresa Strzelecka

August 12, 2005